Mike is a social professor of medicine and internal medicine and medical oncology. He shares patients or cancer patients. As part of the smiling prostate, your logic cancer program. Alright, joining Allen 2009 Doctor Hertz was instructor of medicine at Harvard and attending physician in medicine at the Massachusetts General Hospital. MIKES graduate of Harvard College. He received his doctorate degree in cell biology from Rockville University’s and his medical degree from Cornell University.
He completed a fellowship in Archology, Dana Farber and postdoctoral fellowship in Biology, the Masters in Massachusetts, Channel MIT Institution might still be talking about the silk yellow cell therapy program for solid tumors. Mike take it away. Thanks, Dan. Yeah, thanks everyone for inviting us from that from the therapy dog to talk. I’m going to talk obviously about the solid tumor side and then the other half is going to be here as this would be talking about liquid.
So were the newest art.

And we really started right before covid so we don't have a whole lot of trials open, so I think that this talk is going to be sort of short on data, but I hope it's going to be long on potential.

So the main therapies I'm going to talk about today are car T cells and tumor infiltrating lymphocytes. I know that a lot of people know somewhat familiar with these terms.
a lot about these so far, but they’re really quite different therapies,

So adaptive immunity is where T cells primarily recognize things that are foreign and used in attack them.

Now,
one of the reasons we don’t attack ourselves is that we’re always taking little chunks of our proteins, expressing them on the surface in something called the major histocompatibility complex, and the T cell receptors. Basically, when were you know your own a little bit? After that all the T cell receptors that we have the T cells. That that recognized groups. That recognize. The energy is well, get deleted,
or at least they get turned off OK, so generally we don’t respond to our own antigens, But if you get a foreign antigen like a bacteria, what happens is let’s say if they go into a cell, the cell chops up the proteins. The proteins get put on MHC and the T cell receptor is going to recognize there’s going to be a strong interaction, but that isn’t enough to actually cause killing. It’s only when you get something
called costimulation OK,
and that's via another pathway.
Another set of receptors.
And then you actually get killed all right.
So how can we use that information
to kill cancer cells?
So let me say a little bit more and
go a little bit more in depth into
the T cell receptor signaling first.
So this is a schematic of
the T cell receptor,
the Alpha beta chains are the ones that
actually recognize the antigens and MHC,
and there are signaling molecules,
the Zeta chain and the associated CD3.
So T cell receptors only recognize proteins.
They only work if the antigen is expressed is presented by MHC. And they require Co stimulation. And as I said, the signaling are through these two things. Antibodies another way that we recognize things that are formed were quite differently. They can recognize any type of management doesn’t have protein. They don’t use MHC, and antibodies are much, much stronger, their interactions with their antigens and T cell receptors are with their antigen that makes the interactions up.
00:03:49.743 --> 00:03:52.279 to 1000 and 10,000 fold stronger in fact.
NOTE Confidence: 0.8157049
00:03:52.280 --> 00:03:53.900 So someone had the bright idea
NOTE Confidence: 0.8157049
00:03:53.900 --> 00:03:56.032 of taking the back end of a T
NOTE Confidence: 0.8157049
00:03:56.032 --> 00:03:57.272 cell receptor and connecting it
NOTE Confidence: 0.8157049
00:03:57.272 --> 00:03:59.175 to the front end of an antibody.
NOTE Confidence: 0.8157049
00:03:59.180 --> 00:04:01.343 And we call those guys get chimeric
NOTE Confidence: 0.8157049
00:04:01.343 --> 00:04:03.099 antigen receptors and so this is
NOTE Confidence: 0.8157049
00:04:03.099 --> 00:04:04.629 the first generation car and this
NOTE Confidence: 0.8157049
00:04:04.629 --> 00:04:06.140 is actually in the 1990s.
NOTE Confidence: 0.8157049
00:04:06.140 --> 00:04:08.750 It was awhile ago so this is the antibody.
NOTE Confidence: 0.8157049
00:04:08.750 --> 00:04:10.814 OK on the outside of the cell and
NOTE Confidence: 0.8157049
00:04:10.814 --> 00:04:13.098 this is part of the solar spectrum.
NOTE Confidence: 0.8157049
00:04:13.100 --> 00:04:15.710 The inside of the cell worked a little bit,
NOTE Confidence: 0.8157049
00:04:15.710 --> 00:04:17.258 but not terribly well.
NOTE Confidence: 0.8157049
00:04:17.258 --> 00:04:19.193 A huge breakthrough though came
NOTE Confidence: 0.8157049
00:04:19.193 --> 00:04:21.148 in the second generation.
And here what was done is they add a domain to the protein of CD 28. And what’s that? Whoops, that of course is the costimulatory signal, and so when you put the customer let costimulator right in it, these are much, much more powerful, these are really what we mostly use today. There are even stronger ones. The third generations that use two costimulatory signals, and there’s the 4th generation, which is a combination of cars plus other genes that are put in.
00:04:48.765 --> 00:04:50.787 to make the cells work better.
NOTE Confidence: 0.8157049
00:04:50.790 --> 00:04:53.300 So.
NOTE Confidence: 0.8157049
00:04:53.300 --> 00:04:55.256 When you actually the mechanics of
NOTE Confidence: 0.8157049
00:04:55.256 --> 00:04:57.569 this and in patients are complicated,
NOTE Confidence: 0.8157049
00:04:57.570 --> 00:04:59.706 just like all cell therapies are,
NOTE Confidence: 0.8157049
00:04:59.710 --> 00:05:01.130 whether it’s transplant or
NOTE Confidence: 0.8157049
00:05:01.130 --> 00:05:02.195 something like this.
NOTE Confidence: 0.8157049
00:05:02.200 --> 00:05:05.760 In this case you need to isolate the T cells.
NOTE Confidence: 0.8157049
00:05:05.760 --> 00:05:08.070 They have to get activated and then
NOTE Confidence: 0.8157049
00:05:08.070 --> 00:05:09.893 their transduced with the chimeric
NOTE Confidence: 0.8157049
00:05:09.893 --> 00:05:11.808 antigen receptor and then expanded
NOTE Confidence: 0.8157049
00:05:11.808 --> 00:05:14.041 and then rein infused in the meantime
NOTE Confidence: 0.8157049
00:05:14.041 --> 00:05:15.751 patients get lympho depleted and
NOTE Confidence: 0.8157049
00:05:15.751 --> 00:05:19.268 the reason for that is that.
NOTE Confidence: 0.8157049
00:05:19.270 --> 00:05:20.155 Probably twofold reasons.
NOTE Confidence: 0.8157049
00:05:20.155 --> 00:05:21.040 For some reasons,
you're actually treating the cancer to some degree by lympho depleting, but that isn't the case for all cancers. For some, you're doing it to have a niche for the T cells to actually live in and grow it. As you might imagine, this does not take a day. This takes several weeks, so one of the things about this kind of treatment is patients have to be well enough to survive those weeks and to be able to tolerate the therapy. I'm not going to go into this in detail, but there are a lot of toxicities.
associated with these treatments.

The three famous ones are cited kind of release syndrome,

which has to do with a lot of T cells at the same time,

seeing antigen and then causing lots of cytokines to go into the circulation.

There’s also neurotoxicity called crests or cans and probably the most severe of these HLH.

Alright, So what are we doing at Yale?

We have one party study open right now for solid tumors.

This is a kidney cancer trial done by the company, CRISPR Therapeutics.

It’s anti CD 70 which is highly
expressed on clear cell kidney cancers and then there’s some expression on a few lymphoid type of cells. Now it’s very long name for the trial. The reason is that it’s actually a little more complicated than even what I described before. ’cause these are allogeneic engineered T cells. And what does that mean? So these are T cells that actually don’t come from the patient they come from. Sort of healthy weight healthy donors in whom there they’re having the car put into their own T cells and they this company using CRISPR CAS nine.
I think a lot of us are familiar with that to knock out certain other genes in these T cells to make them work in us. So what do I mean by that? Well, if you take someone else T cells and put them into you, they will attack you and you will attack it. It won’t be an effective therapy. They will get destroyed pretty quickly by the endogenous immune system, and they’re going to have off target effects tube via their T cell receptors, potentially. So what they’ve done this CRISPR therapeutics is in addition to
Putting in the car to these T cells. They’ve also put in using CRISPR. They’ve removed the T cell receptor OK. They’ve also removed something called beta two microglobulin, which is part of MHC class one, and the result is that our immune system doesn’t recognize that it very well except by some something. All natural killer cells. It doesn’t do that much, and it doesn’t really recognize us except via the anti CD 7. Alright, so there are a bunch of advantages here.
of using T cells from someone else and not from the patient one is speed. These cells are waiting. The patients don’t have to wait. Secondly, these cells are for someone with an immune with Acton intact immune system and a lot of patients with extensive cancers may not have intact immune systems and the T cells may be somewhat dysfunctional, and obviously it leads to the potential for more of a drug, something that can be done with high levels of production out there for everybody we’ve enrolled.
One patient, we’re going to be enrolling one patient another patient in a few months, or at the dose escalation phase, and we’ll see how this trial goes. What else is going on at yelled, oh, oh, sorry before I go there, let me just. Say that So what? Some of the challenges are for car T cells. Specifically in solid tumors. Well, in general there can be an issue with persistence. The car T cells. They may not last, but these are big issues for solitaire.
So one there is almost no answers in a solid tumor cannot lose. And when you give something like CAR T therapy against a particular antigen, it’s very likely that the tumor will just mutate or lower expression of that antigen. And become resistant to it. In addition to that, the micro environment of the tumor is very toxic to a lot of immune cells, including T cells. It’s hard to infiltrate into a lot of tumors. There’s a lot of necrosis. Many of the cells have low blood supply, etc.
And finally, the toxicity is that I sort of mentioned before. So one of the things that's being done here is being done by the lab of City Chen. His is the only 11 going to talk about, but it's worth pointing out there are many labs here working on car T type therapies. City Shuns Lab has developed a modular, high throughput way of developing cartis, and it's the system that again is very complex. There's a there's no time for me to describe it and be I.
wouldn’t be able to do very well anyway.

But this is a slide from from CD,

this is his own system that he is

designed using adeno associated virus.

To make parties,

it enables rapid building of new

modules because because modular we

can put in many different cars into a

lot of cells and look at them in parallel.

And it also allows for knockout

And it also allows for knockout

of other genes in the cell just

to make to try to improve the

cell’s capabilities.

And therefore we’re looking for

is superior cancer killing based
on a lot of the platforms that are used now in the short term goal, of course, is to generate better parties against kidney cancer. He’s actually looking at kidney cancer, which is great. ’cause that’s a lot of what I’m interested in, and we’re also working with Doctor Krueger on this area. Cougar, but also he can engineer in safety control so that if the T cells are causing some of these severe toxicities, they can be turned off. And you know the long term goal, of course, is to optimize better
parties across solid tumors.

Anan maybe liquid tumors too.

In the first step of that,

but he makes a great car.

Is for us to actually put

moving on to till let’s go back

very quickly again into immunity.

So remember something for and it’s

a strong interaction by the T cell

receptor and the MHC complex you get

Co stimulation and you get killing.

Alright,

but how do you get a T cell that actually

kills something that’s not for it,
As mentioned before, we don’t interact very well with our own antigens. Now, cancer has sort of solved that a little bit for us in that cancer proteins are often mutated because cancer causing mutations and therefore the peptides actually can look for and so you can actually get T cells to kill. As we all know though, it doesn’t really work very well on its own. We need to give things like immune
checkpoint inhibitors because of the toxic micro environment, so I thought that was developed back in the 1980s. Was well, maybe if we take the two T cells out of that environment, grow them up, enhance their function with cytokines, maybe we can cause cell killing if we re infuse those T cells. And that’s what ’til therapy is. So much like I described, the car T cells, you respect the tumors from patients. T cells are isolated from those tumors. They are activated and expanded in vitro,
NOTE Confidence: 0.8152212
00:12:20.520 --> 00:12:21.948 generally using Interleukin 2,
NOTE Confidence: 0.8152212
00:12:21.948 --> 00:12:24.090 but there are other interventions we
NOTE Confidence: 0.8152212
00:12:24.151 --> 00:12:26.495 use and then they reinfuse with the patient.
NOTE Confidence: 0.8152212
00:12:26.500 --> 00:12:27.493 In the meantime,
NOTE Confidence: 0.8152212
00:12:27.493 --> 00:12:29.148 agents have been limited depleted,
NOTE Confidence: 0.8152212
00:12:29.150 --> 00:12:31.496 which is extremely important for this
NOTE Confidence: 0.8152212
00:12:31.496 --> 00:12:33.953 therapy because we not only have to
NOTE Confidence: 0.8152212
00:12:33.953 --> 00:12:36.460 have a niche for the cells to go into,
NOTE Confidence: 0.8152212
00:12:36.460 --> 00:12:39.826 we have to get rid of T regulatory cells.
NOTE Confidence: 0.8152212
00:12:39.830 --> 00:12:41.050 And the Immune system Act
NOTE Confidence: 0.8152212
00:12:41.050 --> 00:12:42.270 as a sighted kind sink,
NOTE Confidence: 0.8152212
00:12:42.270 --> 00:12:44.111 sucking up all the good side accounts
NOTE Confidence: 0.8152212
00:12:44.111 --> 00:12:46.170 that we want to go to these T cells.
NOTE Confidence: 0.8152212
00:12:46.170 --> 00:12:48.662 'cause when we infuse these T cells
NOTE Confidence: 0.8152212
00:12:48.662 --> 00:12:50.828 we give patients in alluding to.
NOTE Confidence: 0.8152212
Now before I move on with that with till I think a lot of the time when I tell people that were interested in cell therapies, they say oh it’s cortisol therapy. But there’s a huge difference is really between CAR T cell therapies and tilsen. I think of them is really entirely different. As some examples. You know, car T cells are MHC totally independent right there using an antibody, whereas ’til therapy is totally dependent. CAR T cells don’t? They can look at sugars or other non protein antigens. Tills do not.
Cars are pretty ineffective at looking at intracellular proteins. They’re working on that, so maybe we’ll get there one day, but right now they can’t really recognize a lot of the proteins. And the key thing is that you know, till can look at any antigens that they see. So for example, when we take tumors out of patience and isolate the lymphocytes from those, that’s going to be a diverse, diverse type of T cells, probably recognizing multiple different antigens.
And, as I said before, a big disadvantage of car T cells. Is that you can lose the one antigen they recognized in their useless and that may not be as big issue with 'til therapies. And Lastly, there toxicities are quite different. Alright, So what are we doing at Yale? We have a trial right now for looking at triple negative breast cancer. This is an IIT that I’m doing with IMS Therapeutics. This is the first dedicated breast cancer till trial world we’ve been. We’ve enrolled two patients so far,
and one of the reasons were interesting.

Breast is that there’s lab here.

Tristan Park, who’s a surgical oncologist here, an expert on breast cancer and on breast cancer cell therapies?

Looking at the samples we get analyzing for the immune infiltrates and working with us on the trial. Just to say a little bit more about what it actually entails. It’s there’s a lot of for any sort of cell therapy. There’s a lot of work that goes into
because these are complicated therapies that require a good timing so you know once a patient signs consent, they have to get their surgeries. Only then do you initiate. Of course the till culture, then it’s going to be going for several weeks, and once you know the till is growing appropriately, only then are you going to limited Lee the patient and then infuse that into the patient. And then of course, as I said, these people require oil to afterwards,
and they’re going to be in the hospital for a lot of this because they’re going to depleted and then once they recover, we follow them.

So, how might we improve some of these things? I think infusion and reception isolation. That’s not where the money is, but clearly we can maybe improve activating and expanding these cells and make them better killers. And the people who are the best at growing up and activating these cells.
Of course that you are the people of the Advanced Therapy Lab run by Alexi Burst. Never die across and they have a huge amount of expertise over many years. Looking at till type therapies. They’ve grown up a lot of different cell products for use in patients, and I actually hold Inds for growing Melanoma till, but of course they actually did it and we’re working together right now to grow up lung cancer till four, ideally to eventually put into patients. Just quickly to point out, they are very good at growing up selves.
This is 1 experiment which they actually separated out the PD one positive from negative cells and show a lot of expansion in both of them and this just kind of shows one experiment of theirs that the cells they get are actually quite good. So here till they’ve isolated out and these are assays for interferon gamma production which is an essay of sort of it’s a surrogate for cell killing and when you take this pill and you put him. Alone, they don’t make a lot of interferon gamma.
As soon as you put them with autologous tumor, or they recognize antigens in the setting of MHC, they make tons of interferon gamma and then if you give them someone else's tumor that has emerged, they don’t recognize they don’t kill. So they’re very good at making cells that kill and kill specifically, which is exactly what we need.

So what can we do to actually improve things? To make these, what are we interested in doing here? Yale to improve these therapies? Well, the South therapy the AC T lab is
00:17:17.387 --> 00:17:19.709 doing experiments to look at adjusting

NOTE Confidence: 0.89995277

00:17:19.709 --> 00:17:22.594 the growth medium that that they do

NOTE Confidence: 0.89995277

00:17:22.594 --> 00:17:24.739 it in different cytokine combinations, 

NOTE Confidence: 0.89995277

00:17:24.740 --> 00:17:26.590 different levels of cytokines and 

NOTE Confidence: 0.89995277

00:17:26.590 --> 00:17:28.070 those experiments are ongoing. 

NOTE Confidence: 0.89995277

00:17:28.070 --> 00:17:29.895 But. It’s actually striking how 

NOTE Confidence: 0.89995277

00:17:29.895 --> 00:17:32.093 little we know about what happens 

NOTE Confidence: 0.89995277

00:17:32.093 --> 00:17:34.200 between when we take the cells out 

NOTE Confidence: 0.89995277

00:17:34.200 --> 00:17:36.537 of a person and we expand them. 

NOTE Confidence: 0.89995277

00:17:36.540 --> 00:17:37.808 We don’t really know 

NOTE Confidence: 0.89995277

00:17:37.808 --> 00:17:39.076 which cells get expanded. 

NOTE Confidence: 0.89995277

00:17:39.080 --> 00:17:41.792 We don’t know whether the T cell maturation 

NOTE Confidence: 0.89995277

00:17:41.792 --> 00:17:44.170 states whether they are more naive or more. 

NOTE Confidence: 0.89995277

00:17:44.170 --> 00:17:45.442 Effector cells dictate which 

NOTE Confidence: 0.89995277

00:17:45.442 --> 00:17:46.396 cells that expanded. 

NOTE Confidence: 0.89995277
We don’t know how this concept of T cell exhaustion relates to expansion, and we have very little idea about how homogeneous or heterogeneous that essential traits are between tumors or between tumor types. So and can we. Can we actually do experiments to figure some of this stuff out? And the approach that we’re going to take here, and we’ve actually begun taking, is to do single cell RNA sequencing and paired with TCR sequencing so that we can follow specific T cell clones through growth and figure out how they evolve.
out which maturation phenotypes are the ones that grow the best. And whether exhaustion has an effect, one is being done beginning, and Sam Katz is lab by Sam Kerr, one of his graduate students, and I'll be doing some of these studies on long till. But really, the person doing this, Ben Lewin, the Hafler lab. I have no time around this,
so I don’t know where I am on time and
someone told me I’ve got a little time.
OK,
So let me say one last set of experiments that are being done at Yale.
Looking at some basic science that could have a big impact on T cell therapies.
And by the way, I should point out that, you know, I’ve mentioned a few people who are doing work,
but there are many others doing work at Yale.
I they don’t have time unfortunately,
but I don’t mean to leave other people out.
We’re doing really vital stuff that
in fact probably there are a lot of things I don’t know about that. I wish I did.

So one of the things that Sam Katz’s lab is working on for quite awhile. So some invoices lab is Weismann’s lab is working on is the idea of M RNA reprogramming? So he’s using something called crisper I which is a crisper based technique to knock down genes but not to actually cause mutations or changes the actual DNA. The advantages of this technique is that you can do multiple RNAs at once.
00:19:46.250 --> 00:19:49.045 Sorry bout that. The.
NOTE Confidence: 0.83190864
00:19:49.045 --> 00:19:51.055 Other thing about this of course
NOTE Confidence: 0.83190864
00:19:51.055 --> 00:19:53.710 is when you do these things by RNA.
NOTE Confidence: 0.83190864
00:19:53.710 --> 00:19:54.544 RNA is temporary,
NOTE Confidence: 0.83190864
00:19:54.544 --> 00:19:56.212 so there are pluses to that
NOTE Confidence: 0.83190864
00:19:56.212 --> 00:19:57.460 and minuses to that.
NOTE Confidence: 0.83190864
00:19:57.460 --> 00:20:00.196 The pluses are that it’s a lot safer.
NOTE Confidence: 0.83190864
00:20:00.200 --> 00:20:01.528 Not permanently altering itself.
NOTE Confidence: 0.83190864
00:20:01.528 --> 00:20:02.856 OK, the negative, however,
NOTE Confidence: 0.83190864
00:20:02.856 --> 00:20:04.516 is that it’s only temporary,
NOTE Confidence: 0.83190864
00:20:04.520 --> 00:20:06.725 so if you want to have effects
NOTE Confidence: 0.83190864
00:20:06.725 --> 00:20:08.499 that last a long time,
NOTE Confidence: 0.83190864
00:20:08.500 --> 00:20:12.865 this might not be the method to do it.
NOTE Confidence: 0.83190864
00:20:12.870 --> 00:20:15.054 But you can imagine situations where using
NOTE Confidence: 0.83190864
00:20:15.054 --> 00:20:17.462 this kind of technique you could really
NOTE Confidence: 0.83190864
00:20:17.462 --> 00:20:20.089 turbocharge a cell for short period of time.
So for example, we could have a car T cell. And you could use his technique to make the groups make them particularly proliferative at the time at inside accounts, for example to happen particularly powerful and killing stimulators of other things, you could have inhibitors of negative regulators, and in fact Sam is shown in his lab and from Weismans lab that for example they can at the same time using their CRISPR RNA I techniques, Christmas learning techniques.
to increase IL two in a cell.

And decrease BCL type proteins which are made up tatic proteins.

So again when you think about what I’ve talked about so far with, let’s say the city Chen Lab in which they can do multiple different things to design sort of permanent T cells, that car T cells that are particularly powerful.

You could also imagine adding in these M RNA’s to those same cells and making turbochargers even more so.

There’s a huge amount of combinatorial things that we could do.

To improve his cell therapies,
and there’s a lot of excitement for all those things.

Last but certainly not least, I just want to acknowledge all that people have been doing a lot of work.

So what first assault therapy DART 3 docs? Who do it right now or are nearest Stewart and I Alex is our CDT as fantastic Sharon days.

Who do it right now or are nearest research nurse Ann Pavan or CRA.

I’m not impressed but and then we have an amazing team here doing,

you know regulatory and pharmacy etc.

Also, of course, the AC T lab.
Which you know is really going to be the people developing.

Sorry the next therapies that we do here, I mentioned the Melanoma team because, really, we’ve been doing till at Yale for very long time. And the person who got us started here was Mary Otional and a lot of the ideas that I talked about with regards to how to study these things really came from Mario. Harriet has done the most to have anybody here and has done a huge amount and Sarah Weiss has seen. A lot of the patients as well,
Katrina Bezak, is the person who is really a point person for a lot of salt therapies here, and she’s actually also key for setting us up for. As I said, the very very likely approval of heart till in Melanoma people probably don’t know this, but we have our own something called CDC which is for cell therapies. It’s a committee to look at really usage and whether we have the capability and the capacity. To do all the different trials we want to do,
none of this would be possible without the nursing staff on 11/12 North.

A pheresis machine, Hendrickson the RSL, Audrey King, and of course, the lab.

As I mentioned, and I should point out, that as I said, we're trying to get an Ind right now for long till.

And that's based on funding we got from the office floor, and I think I'll leave it at that.

Thanks everybody.

My great presentation. Really excellent.

Let's see if there any questions from the audience chat room here.

So this is from God.
Looks like you’re so excited.
Talk research on adding tablets and margin molecules or modules in T cells to get around challenging metabolic environment for exhaustion times.
So there are there have been, you know, a lot of studies in mice that are really fantastic. Actually, some of the best ones. I think we’re from Sue Keck, used to have a cancer biology lab cancer Menology lab here and now she’s at. Assault or or scripts. I don’t know which, but she’s in California, but absolutely.
So there’s no question that in mice you can knock down metabolic certain metabolic pathways, making T cells much more tolerant of the toxic micro environment in the tumor. Now that hasn’t yet been done in people. I don’t think, or I should say, it’s not entirely true. People have been doing screens to look at to make T cells more effective, and either party or till, and so there might be a company out there that has done that, or we just don’t know. But absolutely, that’s a huge area of research
by a lot of people, and I think we will definitely at some point the future be seen. Carty cells that have metabolic pathways altered based on this. This is some recent data looking Dyson kinase and using that as a way of overcoming, I'll. There being no troubles me design right now. Look at this picture. Next comment is from Marcus Poison Bird. Next comment is from Marcus Poison Bird. Nice presentation, just to mention. Let’s try this myself. Every efforts include developing
Massapequa tillmanns.
Yes, absolutely.
I need to talk to you.
And Marcus, yes, very excited about that.
Ask questions.
Have party studies been performed
patients in multiple Kartik
loans simultaneously against
multiple different energies?
How many tourists again,
is it generally available?
Is detention targets in
different types of solid tumors?
So I don’t know
the answer to that,
but I can tell you what I do now. So I think the idea of using multiple parties at once. I think there’s a worry that when you do that and I think their data for this that multiple ones within a cell result in a decrement of the actual response that you need to have. A lot of the same. You need to have sort of. The same cars activate it all at once to really get a good response. We have too many androgens. It doesn’t, I think, work as well like you basically.
dilute out the response.

That's what I think.

He basically diluted out.

Now there are have been people who are designing right now parties that are.

Their heritage, their heterodimers, so one of the antibody chains is to one target.

One of the antibody chains to another target that's only going to work if you have really high levels of both antigens.

Obviously on the cell, but those are inexperienced or those are being experimented on right now and we'll see how those work.
There's a real question about if you do that, you're not going to get the binding is not going to be as good regarding the number of tumor specific antigens. Again, it probably varies from cell to cell. That the older studies seem to indicate that these are very old studies, so it’s very hard to know what that means. But for the till studies in some of the patients, when I looked at the ones who had really good responses. It did look as though. It was usually one dominant clone. Sometimes there were two dominant clowns.
It’s hard to know exactly what those data are. Was there a very limited number of patients, and it’s hard to know that they were looking at the right time. Like maybe the clone was there did a lot of what it’s supposed to do, and then a lot of it disappeared from the blood for some reason, so it’s very hard to know how much that’s real. The last thing I would say, though, is that it looks as though the most important antigens are private neoantigens, meaning they’re not these big targets that we do, and that’s really a worry.
for car T cells in general,
for solid tumors.
So that is sort of a separate issue.
Terrific Mike is always great presentation,
so like to move on to our second speaker,
Doctor IRA, Sufi doctor Susan,
System Professor of Medicine and Hematology Co.
She received her medical emergency nurse in New York at Stony Brook
and completed a fellowship at Yale
University School of Medicine.
Doctor seems clever work is in the area of hematological in season.
Tallest algic stem cell transplantation

for his commissions as part of New Sweden legacy programming transplant teams.

She developed a strong interest in the president, promised she’s focused her efforts in treating patients with aggressive, more focus as part of clinical trials solid in the response to treatment without August or outdated.

Translate based on the specifics of specific seeds.

As to director of the car T cell therapy product Spell Cancer hospital doctor Soupy.

As part of a team that brings interview Milliman therapy treatments
00:29:17.623 --> 00:29:19.373 options to patients with certain
types of blood cancers doctors.

00:29:22.460 --> 00:29:24.728 Thank you very much for having me.

00:29:36.100 --> 00:29:37.360 Can you see my slides?

00:29:51.770 --> 00:29:53.358 Sorry, just have to share.

00:30:15.820 --> 00:30:16.290 Yeah.

00:30:19.060 --> 00:30:19.999 Yep, that’s great.

00:30:22.050 --> 00:30:24.654 Thank you so my focus today is
 going to be in South therapist

00:30:24.654 --> 00:30:27.358 going to be in South therapist

00:30:27.358 --> 00:30:30.340 for him to logic malignancies and

00:30:30.340 --> 00:30:33.585 and what we’re doing here at Yale.

00:30:33.590 --> 00:30:35.810 I’m a clinical investigator in

00:30:35.810 --> 00:30:37.586 lymphoma and cell therapies.

00:30:41.590 --> 00:30:44.908 I have a couple of bad disclosures.
So the I’d like to update you today on some of the FDA approved indications for cell therapies and he malignancies, which are growing by the day. Some of our research strategies to improve response rates and prevent resistance to cell therapies. Some of the challenges we’re facing clinically and research wise. And then I’d like to end the presentation by. I’m giving you an idea about the work that we’re doing here at DL as part of our immune cell therapy dart for hematologic malignancies and then some of the Inter institutional research collaborations that we
have started to work on.

So, as Mike mentioned, there’s been an evolution in chimeric antigen receptors. Over time, the once we are still using in the clinic that are commercially approve, our second generation cars, but there is some innovative card design going on including suicide cars as a control mechanism for better toxicity management. This dual targeting cars that express. Two different antigen specific cars by specifics where you have.
Add two linked SF Sfes within one core vector and then these TCR mimic cars that are important to address HLA presented antigen swear. You're directing the CFP domain against a peptide HLA complex. Initially the target was CD 19 for B cell malignancies because as you all know it’s a pan bissan marker, its expression is generally restricted to B cells and their precursors and represent it’s surface molecules, so it’s represented irrational target for therapy and he malignancies and so all of the agents that are approved for commercial use.
Or directed at city 19. So we started initially back in 2019. The first approval with that DISA, gentle occlusal in pediatric LL and subsequent to that we’ve had a series of approvals including this agenda, Cluzel and Axicabtagene Silo Loosle for aggressive diffuse large B cell lymphoma, transformed follicular lymphoma and then Lisso catagen merilou. So where you are giving the cells differently because it’s a defined CD4 to CD8 ratio, there is some novelty compared to the two previously approved products and then more recently Brexit.
catagen auto loosle just in the last year for mantle cell lymphoma.

Anan, finally, you know just a few weeks ago Axicabtagene Silo Loosle for relapsed refractory follicular lymphoma. So the response rates that we see with these drugs, particularly in low grade lymphomas like follicular, are extremely good with very high overall response rate and complete response rates in pretreated patients, and then in diffuse large B cell and aggressive deal BCL or transformed the complete response
rates have varied anywhere from 30 to 50% even though the initial overall response rates.

Are very high, so these are still very good outcomes. Don’t get me wrong for this group of patients, you know the predicted long term. Survival is typically less than 10% when they go on to get CAR T cell therapies. So we’ve really been able to cure a good subset of those patients.

But as you can see, you know we still have a long way to go in aggressive lymphomas because.
Even of the patients were cheap

complete remission only about 2/3 are able to maintain that, but it’s very.

It’s very exciting because just in the last couple of years we now have all of these products that are commercially approved for use and that we are already using here at Yale.

So the other rational target was BCM may in multiple myeloma, which is highly expressed on malignant plasma cells. And we know that higher concentrations of soluble BCM mayor also associated with poor outcomes in multiple myeloma.
This is very essential in regulating B cell maturation and differentiation.

And so there have been a series of phase one and two studies looking at PCM. A directed car T cells. And particularly the first one I did, captain be cluzel, is actually very close to approval. These were very heavily pretreated patients with a median number of treatments being about 6.

And as you can see, the overall response rates are extremely good and even complete response rates.
Are are very good and so.

There is of course toxicity like we saw with anti CD 19, particularly cytokinin release and neurologic toxicity, but again this is a very difficult population of patients to treat. The majority of them were what we call triple refractory to emit proteasome inhibitors and about 25% proteasome inhibitors and about 25% of patients were pent. Artifactory.

These are extremely good outcomes for this. For this patient population. And there’s now a race to get FDA approval in the USA.
Not just only for I decapped agenda cluzel but but also for. For several other products and there are efforts being made to introduce them earlier in earlier phases of disease and comparing them to the standard of care which is autologous stem cell transplant. And then there are already efforts being made to mitigate antigen escape by combining. For example, PC MA Carty with CD19 CAR targeting other other antigens. So the same cannot be said for acute myeloid leukemia, unfortunately, which has been, you know,
a great challenge over the years.

And because many of the potential target antigens are actually intracellular,

their tumor associated antigens or NEO antigens and.

And the proteins that are expressed on the surface of the malignant leukemic cells,

like City 33,

you know some of those markers are also expressed on.

Hammer away **** stem cells and so.

The trials going on have had to consolidate.

Cortisol therapy or or rescue I

should say the the mirror with an allogeneic stem cell transplant.

So there are several critical
and resolved issues with car T cell therapy in malignancies, and I would categorize them in failure to achieve remission, disease, relapse, toxicities with car T cell and then some of the toxicity. Some of the challenges in moving beyond Bissell LL and diffuse large B cell lymphoma, two other diseases that may not necessarily. Have high expression of surface markers. Easy to visit that are easy to target with cortisol therapy or certain diseases where. Malignant clone, residing inside a lymph
00:39:43.050 --> 00:39:46.169 node and not necessarily in the circulation.
NOTE Confidence: 0.77998555

00:39:46.170 --> 00:39:49.466 Like with Abyssal LL and so there’s that
NOTE Confidence: 0.77998555

00:39:49.466 --> 00:39:52.012 challenge of the tumor microenvironment
NOTE Confidence: 0.77998555

00:39:52.012 --> 00:39:55.827 prohibiting the T cells from getting there.
NOTE Confidence: 0.77998555

00:39:55.830 --> 00:40:00.226 So. What is it that?
NOTE Confidence: 0.77998555

00:40:00.226 --> 00:40:03.040 Predicts outcome from a patient perspective.
NOTE Confidence: 0.77998555

00:40:03.040 --> 00:40:06.768 Ann and risk factors that we can outline
NOTE Confidence: 0.77998555

00:40:06.768 --> 00:40:10.208 before they go onto car T cell therapy.
NOTE Confidence: 0.77998555

00:40:10.210 --> 00:40:12.912 So there was this large study that
NOTE Confidence: 0.77998555

00:40:12.912 --> 00:40:15.726 looked at baseline factors that were
NOTE Confidence: 0.77998555

00:40:15.726 --> 00:40:18.351 associated with worse overall survival
NOTE Confidence: 0.77998555

00:40:18.351 --> 00:40:20.717 and progression free survival in
NOTE Confidence: 0.77998555

00:40:20.717 --> 00:40:23.195 patients who got standard of care.
NOTE Confidence: 0.77998555

00:40:23.200 --> 00:40:23.647 Axicabtagene,
NOTE Confidence: 0.77998555

00:40:23.647 --> 00:40:27.223 Sila Loosle and as you can see here,
NOTE Confidence: 0.77998555

00:40:27.230 --> 00:40:30.032 there were several factors that were
00:40:30.032 --> 00:40:31.433 statistically significantly associated.

00:40:31.440 --> 00:40:36.588 With worse outcomes and in particular.

00:40:36.590 --> 00:40:40.294 I would outline here patients that had high

00:40:40.294 --> 00:40:44.039 bulk of disease and patients that had,

00:40:44.040 --> 00:40:45.058 for example,

00:40:45.058 --> 00:40:47.603 elevated LDH levels pre transplant

00:40:47.603 --> 00:40:49.633 patients who required bridging

00:40:49.633 --> 00:40:52.159 therapy also were at higher risk

00:40:52.159 --> 00:40:54.653 of having worse overall survival

00:40:54.653 --> 00:40:56.965 and progression free survival,

00:40:56.970 --> 00:41:00.330 perhaps because both of these things are

00:41:00.330 --> 00:41:03.917 a surrogate for a higher disease burden,

00:41:03.920 --> 00:41:07.070 and then Interestingly some of the other

00:41:07.070 --> 00:41:10.438 factors that were associated with outcomes.

00:41:10.440 --> 00:41:13.065 Were younger age and also

NOTE Confidence: 0.77998555
male gender and and that is.

Very different from what we see.

Included in our prognostic indices

for lymphomas where actually

older patients tend to do worse,

and this means that we need to really,

really look at our prognostic markers

in the era of cell therapy and

really redefine what relevant

clinical risk factors are.

So this is showing a multivariable

model of Afexa cottage inside

a looser treated patients,

Poor performance status and

also having high elevated,
high LDH levels is associated with worse progression, free survival and overall survival.

And then what about the disease itself? One of the things that we already know is that about 25 to 30% of patients who relapse after car T cell therapy experienced loss of CD 19 and this was demonstrated. So it’s not the majority of patients, particularly in lymphoma, but it is a good subset and so you know what.
What can we do?

To prevent antigen loss and then also this PD One PDL,

Because we know that PDL one up regulation is actually contributing to Carty exhaustion so.

We have this publication nice publication in Nature Medicine from 2020, where.

Nirav Shah at Wisconsin, actually looked at point of care manufactured by specific anti CD 20 and anti CD 19 CAR T cells in relapsed malignancies.

In some of these patients had already undergone anti CD 19 CAR T cell therapy.
And they do see ongoing responses in about 40% of patients, I think out of about 60% that responded initially and they did not observe loss of CD 19 in progressing patients when they. So really very very exciting data. And then just this year. Just this past year at ASCO. They presented results of a first CD 19 and CD 22 targeting Bicistronic which is dual antigen targeting. With humanized binders, to reduce image unicity, and in addition to 41 BB costimulatory,
00:44:25.770 --> 00:44:31.346 they also edit OX 40 to improve persistence.

00:44:31.350 --> 00:44:35.550 So based on that?

00:44:35.550 --> 00:44:38.214 Data they went on to do a single

00:44:38.214 --> 00:44:40.908 arm open label multicenter phase.

00:44:40.910 --> 00:44:44.151 One two study where they did tool

00:44:44.151 --> 00:44:47.086 dual targeting of CD 19 and CD 22.

00:44:47.090 --> 00:44:50.338 But they also added Pember Lizum app

00:44:50.338 --> 00:44:52.868 for relapsed refractory diffuse large

00:44:52.868 --> 00:44:55.518 B cell lymphoma and Interestingly.

00:44:55.520 --> 00:44:58.148 What they saw is there is a high rate

00:44:58.148 --> 00:45:00.780 of complete response is about 66%,

00:45:00.780 --> 00:45:03.939 although it’s too early to say you know how.

00:45:03.940 --> 00:45:06.088 If they’re going to be durable

00:45:06.088 --> 00:45:08.159 and how durable they will be,

00:45:08.160 --> 00:45:10.668 because right now they.

00:45:10.670 --> 00:45:14.156 They only have short term a data,
Interestingly there was very little toxicity with this particular construct. They did not see any grade three or four cytokine release or neurologic toxicity. And that perhaps really is a reflection of this. Really novel technology that they’re using with a novel pentameric spacer, and this humanized binders so this data is very exciting because it’s a therapy that we might be able to use if approved eventually in the outpatient setting and delivered in the outpatient setting.
going with this. So I'm.

What else do we know about the disease aspect itself that may make response to cortisol therapy. Challenging, so this data from the Juliet study, which was the global phase two trial of tisagenlecleucel in relapsed refractory diffuse large B cell lymphoma. They looked at the Myc expression and tumor infiltrating T cells in that study, and what they actually found was that baseline mic negative status was actually associated with significantly improved outcome compared to Nick positive patients.
And that included also longer median duration of response and overall survival. And when they looked at the tumor microenvironment analysis of the baseline biopsies, what they saw is that lack or low frequency of tumor infiltrating CD 3 positive T cells was also associated with short progression free survival compared to patients that had more than 3% CD 3T cells. In the tumor so taken together, these results suggest that make overexpression or an unfavorable immunosuppressive tumor microenvironment.
with a restricted T cell response may impact score efficacy in patients with large B cell lymphoma.

And then this publication and Oncotarget looked at mutations or copy number losses of CD58 and TP53. Genes in diffuse large B cell lymphoma and showed that these are independent unfavorable prognostic markers so.

This is actually binds CD two and the T cells and T cell mediated cytotoxicity and also NK cell mediated cytotoxicity is actually quite important.

And quite dependent on the expression of CD 58.
On the tumor tissue. So in Ash 2020 they presented data looking at city 58 mutations and circulating tumor DNA is tumor DNA and they showed that this was associated with poor outcome. After Axicabtagene sila loosle. These 358 mutations are common and they occur in about 20% of patients with diffuse large B cell lymphoma and then in addition to that the protein city 58 protein expression is also directly related somewhere between 60 to 80% to 70% of patients with diffuse large B cell lymphoma.
00:49:11.680 --> 00:49:13.785 His do regulate have deregulation
NOTE Confidence: 0.891362
00:49:13.785 --> 00:49:16.830 of the CD 58 protein expression.
NOTE Confidence: 0.891362
00:49:16.830 --> 00:49:19.278 And as you can see here,
NOTE Confidence: 0.891362
00:49:19.280 --> 00:49:22.288 they were able to show that loss of
NOTE Confidence: 0.891362
00:49:22.288 --> 00:49:24.420 this expression was also associated
NOTE Confidence: 0.891362
00:49:24.420 --> 00:49:27.024 with worst outcomes were in blue.
NOTE Confidence: 0.891362
00:49:27.030 --> 00:49:30.208 Here you see 5058 wild type and
NOTE Confidence: 0.891362
00:49:30.208 --> 00:49:33.469 in Red City 58 alteration so.
NOTE Confidence: 0.891362
00:49:33.470 --> 00:49:36.158 Fewer patients that had loss of
NOTE Confidence: 0.891362
00:49:36.158 --> 00:49:38.529 CD 58 expression actually went
NOTE Confidence: 0.891362
00:49:38.529 --> 00:49:41.019 on to achieve complete remission.
NOTE Confidence: 0.891362
00:49:41.020 --> 00:49:43.995 The majority either did not respond or
NOTE Confidence: 0.891362
00:49:43.995 --> 00:49:46.689 they achieved only partial remission.
NOTE Confidence: 0.891362
00:49:46.690 --> 00:49:50.458 And then they went on to to progress,
NOTE Confidence: 0.891362
00:49:50.460 --> 00:49:50.930 unfortunately.
NOTE Confidence: 0.36321577
00:49:56.180 --> 00:50:00.660 So, meisner. Amazing group.
Presented this data very, very interesting this year at ASH where they showed that integrating City 22 costimulation within cars was actually able to overcome City 58 loss in tumor cells and they tried this both insists an entrance and it wasn’t until they integrated it entrance that they saw that they saw these. These results so. This was very eye opening for us because, you know, we used to think that. All of the costimulation is coming from other cells. And we didn’t really realize how.
important actually ceded to City to
NOTE Confidence: 0.36321577
was in car mediated cytotoxicity.
NOTE Confidence: 0.36321577
So City 5862 was a very novel
NOTE Confidence: 0.36321577
axis of car resistance that was
NOTE Confidence: 0.36321577
uncovered through deep correlative
NOTE Confidence: 0.36321577
studies in patients getting cell
NOTE Confidence: 0.36321577
therapies and city 58 loss,
NOTE Confidence: 0.36321577
or mutation pretends a poor outcome,
NOTE Confidence: 0.36321577
but perhaps we can overcome that by
NOTE Confidence: 0.36321577
engineering these cars that integrates
NOTE Confidence: 0.36321577
it is 2 signaling in entrance and
NOTE Confidence: 0.36321577
this is important because City 58
NOTE Confidence: 0.36321577
Lawson mutations are also common in.
NOTE Confidence: 0.36321577
Other cancers in are likely able
NOTE Confidence: 0.36321577
to mediate resistance to other
NOTE Confidence: 0.36321577
cars and immunotherapeutics,
so it could perhaps be applied in other malignancies outside of diffuse large B cell lymphoma.

So I’ve spoken to you about the relapse reflect setting, but we are now doing studies pushing these cellular therapies in the second line, and even in the first line settings,

Uma 12 looked at very high risk patients with high grade B cell lymphoma. With Myc, BCL, two and BCL 6 translocations, and they did pet directed therapy for patients who still had disease after two cycles by PET scan.
They actually went on to get their T cells collected and then receive Car T cell therapy. So these are the results. They saw a very high 85% of the overall response rate with 74% CRS. This is a difficult group of patients for us to treat because oftentimes they do not achieve remission and they progress right through therapy. The car T cell expansion was greater in this study when compared to Zuma one which were. Patients with relapsed refractory disease were treated so so higher quality T cells with higher,
00:53:00.660 --> 00:53:03.548 with higher higher proliferation

00:53:03.548 --> 00:53:05.714 and higher expansion.

00:53:05.720 --> 00:53:07.324 So this has not.

00:53:07.324 --> 00:53:10.229 Obviously it’s not prime time for us

00:53:10.229 --> 00:53:12.314 to change our decision-making and

00:53:12.314 --> 00:53:15.589 move this to to first line therapy,

00:53:15.590 --> 00:53:18.410 but there is definitely improved T

00:53:18.410 --> 00:53:21.149 cell fitness in first line treatment

00:53:21.149 --> 00:53:24.734 and this may be the wave of the future

00:53:24.734 --> 00:53:27.597 when we get more long term data.

00:53:27.600 --> 00:53:31.024 So just to sort of recap for you,

00:53:31.030 --> 00:53:34.414 some of the studies in relapsed

00:53:34.414 --> 00:53:36.106 refractory disease and.

00:53:36.110 --> 00:53:38.606 Also to include some data with

00:53:38.606 --> 00:53:41.110 CLL and mantle cell lymphoma,
as you can see very high overall response rates across the board and then somewhere between 50 and 75% complete remission rates in relapse patients. So where are we going with this? As I mentioned, we’re trying to introduce them earlier in the lines of therapies. So many phase three studies looking at second line for transplant eligible patients, randomizing them to transplant versus Carty and then perhaps eventually in the front line and then in a LL patients looking at patients one or MRD positive after one line of therapy.
And then hopefully some of these phase three data in adults will result in an approval because we still don’t have an approval in a LL for patients over the age of 25.

So what about alginate cars is, as you know, there are some limitations with autologous CAR T cells, particularly in terms of cost harvesting and manufacturing failures and disease really progressing during manufacture, and we can really bypass a lot of that with donor derived.

Sales where we can really reduce the time to infusion significantly and actually
be able to take more patients to Carty. And there's an increased probability of healthy cortisol generation and the convenient of repeat dosing if necessary. So these are some of the investigational allogeneic CAR T cells for him malignancies. Targeting different antigens both in lymphomas AALL, but also in multiple myeloma. This is still early phase one phase two data, but I think that this is going to be the wave of the future in Carty, so I'm going to now shift gears to just briefly talk about our cortisol therapy program here at heel we started our efforts in 2018 and were.
Able to eventually treat our first patients in January of 2019 and then were able to actually achieve fact accreditation after extensive auditing of our program. So this is our organizational chart. As you can see, it includes collaboration between multiple different departments. Physicians nursing program self therapy with Diane and alexianne. We have a really trained group of people being able to freeze the patients and
then and then give the conditioning therapy and manage the toxicities.

So what have we done in the last two years with 357 patients, some of them with axicabtagene, sidlu, We're just starting to actually expand to mantle cell lymphoma and then follicular lymphoma. And we've also treated 11 patients on clinical trial for multiple myeloma with anti BCMAM RNA CAR T cells. And as Mike mentioned there are some there is much less toxicity. But there are also challenges in terms of. In terms of the short life of the M RNA,
and perhaps the need for frequent dosing or maybe introducing this in earlier lines of therapy where patients do not have an extensive burden of disease with a new approval and multiple myeloma expected this year, there’s actually an anticipated significant rise in numbers of patients that were going to be treated. And what that means is that we can collect a lot more data and do a lot of studies on patient samples. So this is the yellow advanced cell
therapy lab and then this is our

immune effector cell therapy dart

that Mike and I call lead and and

we have a team as he spoke about.

I won’t belabor this,

but we wouldn’t be able to do what

we do without their amazing work.

So this is our portfolio.

We have some studies that were

opened and finished accrual,

but as you can see we have a large number of.

Pending studies at the majority of

which are very novel because they

are either by specific cars or their

allogenic cars sitting 19 NK cars and.

You know, really also these comparative

You know, really also these comparative
randomized comparative studies introducing car T cells in the earlier lines of therapy. You know, we really took a set back with Chobit, but we really hope to be able to open all of these studies in the next few months and start enrolling patients. So this is. These are some of our collaborations with Doctor Mina Xuan, Doctor Jordan Pober in Pathology, looking at the vasculature in the human lymphoma nodal micro environment. Looking at these phase cars for low antigen expressing B cell cancers and
then collaborations with City Chen.

So in the interest of time, I will just briefly. As you know, getting the T cells to the tumor tissue and increasing homing is actually quite a challenge for most patients, and there have been several attempts overtime looking at how we can improve homing for lymphocytes. Including cell surface painting, for example, to insert alphabeta integrin into primary lymphocytes, including glyco engineering CAR T cells,
01:00:09.100 --> 01:00:10.084 for example,
NOTE Confidence: 0.84343517
01:00:10.084 --> 01:00:12.544 to enforce E selectin binding
NOTE Confidence: 0.84343517
01:00:12.544 --> 01:00:15.467 because as many of you may know,
NOTE Confidence: 0.84343517
01:00:15.470 --> 01:00:18.333 car T cells do not express sialyl
NOTE Confidence: 0.84343517
01:00:18.333 --> 01:00:21.840 Lewis X and do not bind deselecting,
NOTE Confidence: 0.84343517
01:00:21.840 --> 01:00:24.624 but we can actually achieve enforce
NOTE Confidence: 0.84343517
01:00:24.624 --> 01:00:28.345 their display on human CAR T cells by
NOTE Confidence: 0.84343517
01:00:28.345 --> 01:00:30.570 surface fucosylation and this will.
NOTE Confidence: 0.84343517
01:00:30.570 --> 01:00:34.050 Results in very robust E selectin
NOTE Confidence: 0.84343517
01:00:34.050 --> 01:00:37.068 binding even under conditions of
NOTE Confidence: 0.84343517
01:00:37.068 --> 01:00:40.662 hemodynamic shear and then also gene
NOTE Confidence: 0.84343517
01:00:40.662 --> 01:00:43.224 therapy using genetically modified
NOTE Confidence: 0.84343517
01:00:43.224 --> 01:00:46.584 lymphocytes targeting VEGF or two
NOTE Confidence: 0.84343517
01:00:46.584 --> 01:00:49.272 in highly vascularized tumors.
NOTE Confidence: 0.84343517
01:00:49.280 --> 01:00:51.905 But unfortunately all of this data is
NOTE Confidence: 0.84343517
in mice and we don’t really know what’s happening in the human tumor vessels, and we do not have any idea about the spatial relations of these two of these tumor infiltrating lymphocytes, so the aim of our study is to employ highly multiplexed immunofluorescent imaging of human lymphomas to specially correlate and phenotype. The infiltrating even of sites using formalin fixed and not been embedded tissue specimens, and then we want to apply these results to investigate the informer vasculature in car T patients. Pretreatment and posttreatment.
This is Nathan Paulsen, one of the residents in pathology, and he’s already looked at some.

Or lymphoma tissue samples showing that there are differences in expression levels of vascular adhesion molecules. For example, between diffuse large B cell lymphoma, classical Hodgkin lymphoma and T cell rich large B cell lymphoma. And so we want to do high dimensional phenotyping of these vascular cell markers and looking at all of these, all of these vascular markers and.
the we anticipate to find some
NOTE Confidence: 0.84343517

correlation of the vessel phenotypes
NOTE Confidence: 0.84343517

with the abundance and phenotype of
NOTE Confidence: 0.84343517

the leukocytic infiltrates and to
NOTE Confidence: 0.84343517

correlate there this with the patients
NOTE Confidence: 0.84343517

outcomes post car T cell therapy.
NOTE Confidence: 0.84343517

And.
NOTE Confidence: 0.84343517

If we're lucky,
NOTE Confidence: 0.84343517

we're going to be able to show that
NOTE Confidence: 0.84343517

some two rationale for combining
NOTE Confidence: 0.84343517

these CAR T cell therapies with
NOTE Confidence: 0.84343517

antiangiogenic therapies, particularly.
NOTE Confidence: 0.84343517

And this can be a launching point
NOTE Confidence: 0.84343517

for us to
NOTE Confidence: 0.8898998

actually eventually in the
NOTE Confidence: 0.8898998

future consider a trial.
So this is some of the data from Chalet Sues Lab where he’s using these face cars where.

Targeting specifically low density surface antigen and he’s been able to show that car signaling is different from T cell receptor signaling and that it bypasses certain proteins like latch. And has a different pathway that results in acting polar MIS polymerization compared to TCR signaling, and he’s actually using this information to develop these phase cars on lipid bilayers that he can modulate to recognize low density surface antigens.
So this is again some of the data that he is generated in his lab where he’s been able to show that Corti signaling bypasses this important scaffold protein promoting phase separation and. He’s been able to build this face cars where they contain and you control modality that can leverage domains affecting phase separation to modulate Carty activity recognizing low density surface antigens. He’s constructed Roger B cells expressing low to High City 19 and this is just some very preliminary data that he has showing that this point phase cars display superior
activity compared to control parties.

Again, low against low CD 19 so we are hoping to look now at some of our patients blood samples that have.

Low CD19 expressing malignancy’s either at baseline or following treatment with CD19 CAR T cell therapy and showing how these pace cars will be able to act against these low CD19 expressing tumors.

And then we’re also hoping the future to collaborate with City Chen looking at these dual knock out CAR T cells that he’s.
Engineered in his lab targeting two different antigens on lymphoma cells and and.

Doing PT one knockout.

So this is our. This is our group and.

Dedicated really dedicated group of people and I'm very thankful for their work and I went a little over time so I'm happy to answer any questions.

So I don't think there's any questions on the Chatroom at this point so.

I was thank you for a terrific presentation.

Thank you, thank you.